REMARKS

Upon entry of the present amendment, claims 24-27, 32-34, 47, and 49 will be pending. Applicants have cancelled claims 1-7, 14-24, 30, 31, and 48, without prejudice, amended claims 24, 32, 33, and 47, and added new claim 49. Support for these amendments and new claims can be found throughout the application as filed, e.g., at page 39, lines 2-16, and in the claims as filed, *inter alia*. No new matter has been added.

Pending claim 47 was withdrawn by the Examiner as drawn to a nonelected invention; Applicants note that claim 47 has been amended to depend from claim 33, and request that it be examined with the claims presently under consideration.

Specification

The title and abstract were objected to at page 2 of the Office Action mailed January 2, 2009 (the "Office Action") because they "neither the title nor the abstract indicate screening methods to identify compounds that modulate lREl activity."

Applicants have amended the title to the following:

METHODS FOR IDENTIFYING MODULATORS OF
INOSITOL REQUIRING 1 (IRE1) FOR
MODULATING ENDOPLASMIC RETICULUM (ER) STRESS

The abstract has also been amended, as shown above.

In light of these amendments, Applicants request that the objection to the title and abstract be withdrawn.

Claim Rejections - 35 USC § 112

Claim 33 was rejected as allegedly indefinite; for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office noted that "the limitations of claim 33 are unclear because the claim refers to itself." Applicants have amended claim 33 to correct that error; claim 33 now refers to the method of claim 32. In light

of these amendments, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC 5 102

Claims 24-27, 33, and 34 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Bertolotti et al. (Nature Cell Biology, 2000, 2:326-332).

Applicants note that Bertolotti et al. do not teach or suggest the use of an antibody that binds specifically to the autophosphorylated form of IRE1. This limitation was present in previously pending claim 30, which was not included in the anticipation rejection over Bertolotti et al. Applicants have amended independent claim 24 to recite the use of antibodies that bind specifically to the autophosphorylated form of IRE1, and as the Bertolotti et al. reference neither teaches nor suggests such a method, Applicants respectfully request reconsideration and withdrawal of the rejection based thereon.

Claims 24-27, 30, 33 and 34 were rejected as allegedly anticipated by Ron et al. (US 2003/0224428 A1). The Office stated at page 6 of the Office Action that:

> Ron et al. disclose screening methods to identify agents that alter the phosphorylation of IRE1 using antibodies that bind to the phosphorylated form of IRE1 (see entire document, particularly the abstract, paragraphs 22-26, 38, and claims 1-3 and 14-17). Ron et al. also disclose that agents such as tunicamycin, thapsigargin, and DTT are used to increase ER stress in their model systems (paragraphs 15, 60, 64, 67-83).

In order to anticipate, a reference must be enabling of the claimed invention. Here, Ron et al. provide no specific teaching regarding methods for making antibodies that bind specifically to the autophosphorylated form of IRE1. Rather, Ron et al. provide nothing more than hand-waving discussion of general methods for making antibodies. For the most part, the passages cited by the Office are not relevant; the abstract makes no mention of methods using antibodies that bind specifically to the autophosphorylated form of IRE1, and paragraphs 22-26 relate to methods that are "based on knowledge of the IRE1-mediated processing event of the XBP-1 mRNA," see paragraph 25.

The only potentially relevant disclosure is at paragraph 38, which states that:

> In one aspect of the present invention, the detecting involves contacting the assay system with antibodies specific to the phosphorylated form of the IRE1 protein and analyzing whether there has been any binding between the antibodies and the phosphorylated form of the IRE1 protein. Because the phosphorylation sites on IRE1 are known, anyone skilled in the art can develop an antiserum or monoclonal antibody to detect the presence of the phosphorylated form of the protein in cells using well established assays (e.g., immunoblot, ELISA, immunochemistry). Thus, use of such assays to screen for inhibitors of IRE1 phosphorylation is contemplated by the present invention. Further, the suitable antibodies and detection methods already described above are useful in this embodiment of the present invention.

The Ron et al. application does not describe any specific methods for making such antibodies, nor do they provide any working examples in which such antibodies were made or used. Furthermore, contrary to the statement made in the Ron et al. application, the exact phosphorylation site in the human IRE1 was not known, nor does the Ron et al. application specify at which potential phosphorylation site the antibody should bind. In the region of the protein sequence to which the antibody was directed, there are three serine residues; given their proximity to each other, any of them would have been reasonable candidates. See, e.g., Shamu and Walter, EMBO J. 15(12):.3028-3039 (1996), and Papa et al., Science 302:1533-1537 (2003) (copies attached hereto).

Although in some cases it is relatively trivial to generate antibodies, that was not the case with the present phospho-antigens. Prior to the generation of the PIRE1A antibodies by the present inventor, no other antibodies that bind specifically to the autophosphorylated form of IRE1 had been described. Even today, most if not all of the commercially available antibodies, such as those sold by Novus Biologicals LLC (Littleton, CO; IRE-1 alpha Phosphospecific Antibody: NB100-2323), are licensed from the owners of the present application and are described in the instant application. Applicants also submit herewith a copy of the publication that describes making and using those antibodies, Lipson et al., "Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1." Cell Metabolism. 4:245-254 (2006).

Furthermore, Ron et al. provides no disclosure with regard to a method using antibodies generated by "immunizing an animal with an antigen comprising a peptide having the amino acid sequence CVGRH[pS]FSRRSG (SEQ ID NO:20)," as recited in new claim 49.

Thus, Applicants submit that given the difficulty in generating antibodies specific for the autophosphorylated form of IRE1, as evidenced by the absence of any antibodies other than those made by the present inventors using the specific methods described in the present application, and the lack of any explicit disclosure in Ron et al. regarding which of the many potential phosphorylation sites should be used, there is no enabling disclosure in Ron et al. and thus it is not a proper anticipatory reference.

For at least these reasons, Applicants submit that the pending claims are novel over the prior art and respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102. In addition, as Ron et al. is only citable under 35 U.S.C. § 102(e), Applicants reserve the right to swear behind that reference in the future.

Claim Rejections - 35 USC 5 103

Claim 32 was rejected under 35 U.S.C. 103(a) as being unpatentable over Ron et al. (US 200310224428 Al) in view of Kaufman et al. (US 2005/0250182 Al).

As noted above, Ron et al. fails to provide a sufficiently enabling disclosure with regard to the generation of antibodies that bind specifically to the autophosphorylated form of IRE1, and based on the disclosure of Ron et al. one would not have had an expectation of success in making such antibodies.

Kaufman et al. performed Western blot analysis of IRE1α using a regular anti-hIRE1α-lumenal domain antibody, i.e., an antibody that binds all forms of IRE1α regardless of phosphorylation state, see para. 304, and stated that:

> By western blot analysis, it is possible to distinguish unphosphorylated IRE1 from phosphorylated IRE1 due to the slower migration of the latter on reducing SDS-PAGE. Because the endogenous level of IRE1 expression is very low, IRE1 protein was detected by immunoprecipitation using an anti-IRE1 antibody and western blot analysis using the same antibody.

See para. 330. Therefore Kaufman et al. provides no teaching or disclosure regarding the generation of antibodies that bind specifically to the autophosphorylated form of IRE1, as recited in claim 24. To the contrary, as noted in the passage cited above, Kaufman et al. taught the use of other methods for detecting phosphorylation of IRE1. In addition, neither Kaufman et al. nor Ron et al. provide any disclosure whatsoever with regard to a method using antibodies generated by "immunizing an animal with an antigen comprising a peptide having the amino acid sequence CVGRH[pS]FSRRSG (SEQ ID NO:20)," as recited in new claim 49.

As the combination of references fails to teach or suggest every element of the claimed methods, or fails to provide a reasonable expectation of success in performing the claimed methods, Applicants submit that the pending claims are novel and non-obvious over the cited art, and request withdrawal of the rejection under 35 U.S.C. § 103. In addition, as Ron et al. and Kaufman et al. are only citable under 35 U.S.C. § 102(e)/103, Applicants reserve the right to swear behind those references in the future.

Conclusion

For at least the reasons set forth herein, Applicants submit that the pending claims are allowable, and request early and favorable action thereon. The Petition for Extension of Time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-0259US1.

Respectfully submitted,

Date: July 2, 2009

Janice Kugler DeYoung
Reg. No. 50,429

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945
22103869.doc